REMARKS

The specification has been amended to name the parties to a joint research agreement in accordance with 35 U.S.C. § 103(c) and 37 C.F.R. § 1.71(g)(1). Applicants note that authorization to pay the required fee under 37 C.F.R. § 1.17(i) is submitted concurrently herewith.

Claim 75 has been canceled without prejudice herein. Upon entry of the present amendment, claims 21-38, 40 and 76-93 will be pending and under consideration. Claims 34 and 35 have been amended to correct a grammatical error.

New claims 77-93 have been added. New claims 77-92 correspond to claims 23, 25-36, 38, 40 and 76, respectively, but directly or indirectly depend from independent claim 21. New claim 93 is supported in the specification, *inter alia*, at page 12, lines 10-13; page 13, lines 12-37.

No new matter is added by the amendments to the specification and claims.

INTERVIEW SUMMARY RECORD

Applicants' representative thanks Examiner Marx for the courtesy of the interview on December 8, 2005 in connection with the above-identified application. Pursuant to MPEP section 713.04, Applicants submit the following statements of the substance of interview held on December 8, 2005 between Examiner Irene Marx, Attorney Carolyn Elmore and Barry Quart, Ph.D., President and Chief Scientific Officer of Napo Pharmaceuticals, Inc., the assignee of the present invention, in connection with the above-identified application.

The only outstanding rejection, which is under 35 U.S.C. § 103, was discussed at the Examiner Interview. In particular, Applicants explained the history of the invention and how the Davenport reference could be removed as prior art.

1. Rejection under 35 U.S.C. § 103(a)

Claims 1-38, 40, 75 and 76 are rejected under 35 U.S.C. § 103(a) as being, allegedly, unpatentable over Davenport *et al.*, August 16, 1996, Pediatric Pulmonology, S13, Abstract 34, ("Davenport") taken with Ubillas *et al.*, 1994, Phytomedicine 1:77-106, ("Ubillas"), U.S. Patent No. 4,698,360 to Masquelier ("Masquelier"), U.S. Patent No. 5,043,160 to Wursch ("Wursch"), Remington's Pharmaceutical Sciences ("Remington's") and Applicants' admissions.

According to the Examiner, Davenport teaches the oral administration of SP-303, an aqueous soluble proanthocyanidin polymer composition isolated from *Croton* species, to treat secretory diarrhea in an animal; and that the mechanism of action of the compound involves inhibition of cAMP-mediated chloride secretion. The Examiner further alleges that it would have been obvious to modify the invention of Davenport and Ubillas by providing compositions of aqueous soluble proanthocyanidins for oral ingestion which are formulated to protect the proanthocyanidins from the stomach environment and that inhibit or neutralize stomach acid or which are slow release formulations according to the teachings of Masquelier, Wursch and Remington's. The Examiner additionally contends that the references clearly teach that the technology is well known in the art and that it would have been obvious to provide compositions for treating secretory diarrhea by inhibiting fluid accumulation and cAMP-mediated chloride secretion as demonstrated by Davenport.

Applicants respectfully disagree and submit that none of the references cited, either alone or in combination, render the claimed invention obvious.

Prior to addressing the substance of the rejection and the Examiner's reasoning related thereto, Applicants point out that Davenport does not qualify as prior art under Section 102(a) since the presently claimed invention was conceived and reduced to practice prior to the August 16, 1996 publication date of Davenport. Applicants invite the Examiner's attention to the Declaration of the Inventors under 37 C.F.R. § 1.131 ("Rule 131 Declaration") submitted concurrently herewith. According to the Rule 131 Declaration, the inventors, prior to August 16, 1996, conceived of and reduced to practice a method of treating secretory diarrhea in an animal by administering to said animal a pharmaceutical composition comprising an aqueous soluble proanthocyanidin polymer composition isolated from a Croton species or a Calophyllum species in which the proanthocyanidin polymer composition is formulated to protect the proanthocyanidin polymer composition from the stomach environment. In particular, enteric coated beads of SP-303, an aqueous soluble proanthocyanidin polymer composition isolated from a Croton species, were orally administered to mice with the effect that cholera toxin-induced fluid accumulation in the mice was significantly reduced. As additionally explained in Paragraph 4 of the Rule 131 Declaration, the measurement of the effect a test compound has on fluid accumulation in a mouse given cholera toxin is a well known and art-accepted *in vivo* model of the measurement of the effect the test compound has on diarrhea in animals.

Since the Rule 131 Declaration has demonstrated that the inventors conceived of and that the inventors or persons acting under the direction of the inventors reduced to practice the claimed methods of treating secretory diarrhea prior to August 16, 1996, Davenport is not available as prior art against the claimed methods under 35 U.S.C. § 102(a).

Furthermore, Davenport, and the work reported therein, is not available as prior art under 35 U.S.C. § 102(f) or (g), as the present invention and the subject matter of Davenport were commonly owned at the time the invention was made due to the existence of a joint research agreement between the assignee of the application, Shaman Pharmaceuticals, Inc.[1], and the University of North Carolina, the entities to which the authors of Davenport had an obligation to assign their rights. Co-authors S.E. Davenport and S.E. Gabriel had an obligation to assign any and all rights to the University of North Carolina and co-author Edward Rozhon had an obligation to assign to Shaman Pharmaceuticals, Inc. According to 35 U.S.C. § 103(c)(1), subject matter developed by another person, which qualifies as prior art only under one or more of subsections (e), (f), and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the claimed invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Section (c)(2) of 35 U.S.C. § 103 states that for purposes of this subsection, subject matter developed by another person and a claimed invention shall be deemed to have been owned by the same person or subject to an obligation of assignment to the same person, if -- (A) the claimed invention was made by or on behalf of parties to a joint research agreement that was in effect on or before the date of the claimed invention was made; (B) the claimed invention was made as a result of activities undertaken within the scope of the joint research agreement; and (C) the application for patent for the claimed invention discloses or is amended to disclose the names of the parties to the joint research agreement. In accordance with Section (c)(2) of 35 U.S.C. § 103, Applicants submit (A) that the invention disclosed and claimed in the present application was made by or on behalf of Shaman Pharmaceuticals, Inc. and the University of North Carolina, parties to a joint research agreement that was in effect prior to the date the claimed invention was made; (B) that the claimed invention was

[1] The current assignee of record is Napo Pharmaceuticals, Inc. An assignment of the inventors' rights to Shaman Pharmaceuticals, Inc. was recorded at the U.S. Patent and Trademark Office on August 25, 1998 at Reel 10194, Frame 0568 and on January 11, 2000 at Reel 10489, Frame 0941. An Assignment of Assets from Shaman Pharmaceuticals, Inc. to PS Pharmaceutical, Inc. was recorded at the U.S. Patent and Trademark Office on July 3, 2002 at Reel 13070, Frame 0105. A change of name from PS Pharmaceuticals, Inc. to Napo Pharmaceuticals was recorded at the U.S. Patent and Trademark Office on September 22, 2004 at Reel 15810, Frame 0518.

made as a result of activities undertaken within the scope of the research agreement; and (C) that the application has been amended to disclose the names of the parties to the joint research agreement. Thus, Davenport and the work reported therein is not available as prior art under 35 U.S.C. § 102(f) or (g).

In view of the foregoing, as Davenport and the work reported therein is not available as prior art, Davenport (and the work reported therein) must be removed from the rejection set forth by the Examiner. Thus, in view of the Examiner's indication in the Office Action mailed September 14, 2004 that the claims were allowable over Ubillas in combination with the other cited secondary references, this Section 103 rejection has been overcome and should be withdrawn.

Nevertheless, Applicants wish to reiterate for the record that Davenport in combination with the other cited references does not render obvious the claimed invention. There is no suggestion, much less any teaching in Davenport for the isolated, proanthocyanidin polymer from Croton to be enterically protected in order to be useful for use as an anti-diarrheal agent. Davenport reports the administration by gavage of SP-303 (an isolated proanthocyanidin polymer composition isolated from a Croton species) in $NaHCO_3$ as a delivery vehicle in an animal model of secretory diarrhea, using $NaHCO_3$ alone as a negative control in the reported experiment. The abstract reports that "SP-303, administered by gavage, significantly inhibited fluid accumulation ...whereas ...administration of $NaHCO_3$ alone did not." Davenport further states that "SP-303 may be a effective inhibitor of cAMP-mediated Cl^- secretion and may be acting directly on the CFTR Cl^- channel."

Davenport's disclosure of administering proanthocyanidin in $NaHCO_3$, relative to $NaHCO_3$ alone, to inhibit fluid accumulation in the cholera toxin-induced model of secretory diarrhea, does not render the herein claimed subject matter obvious. Davenport does not suggest to a person of ordinary skill that the isolated proanthocyanidin polymer composition must be formulated to protect the proanthocyanidin polymer composition from the stomach environment. While Davenport happened to use the buffer $NaHCO_3$ to formulate the SP-303 for administration by gavage, Davenport does not teach or suggest what the inventors of the instant application discovered, *viz.*, to be effective for treatment of diarrhea, the proanthocyanidin formulation must somehow be protected from the acid environment of the stomach. Thus, Davenport does not suggest formulating the claimed proanthocyanidin polymer composition to protect it from the stomach environment as a controlled release

preparation or to coat the composition with an enteric coating and, thus, does not render the invention obvious.

Applicants submit that the remaining references cited by the Examiner, either alone or in combination, do not render obvious the claimed invention. All of these references have been discussed in detail in prior responses but are briefly discussed again below. Ubillas discloses that the *Croton lechleri* sap can be administered in milk; however, Ubillas also discloses that the *Croton lechleri* sap can be administered in water or alcohol (Ubillas at page 78, second column), neither of which protect against the stomach environment. Further, Ubillas provides no suggestion for formulating the isolated proanthocyanidin polymer composition to specifically protect it from the stomach environment. In fact, teaching that the sap can be effectively administered in water or alcohol teaches away from the present invention since, from Ubillas, one skilled in the art would believe that proanthocyanidin polymer compositions could be administered effectively without any sort of enteric protection. Thus, rather than making the claimed invention obvious, Ubillas actually teaches away from the claimed invention.

Masquelier specifically teaches sugar coated pills for oral administration (Masquelier col. 6, lines 26-28). Sugar coating readily dissolves in an aqueous environment regardless of the pH and, thus, would not be effective to protect the proanthocyanidin from the stomach environment. In fact, Masquelier does not suggest the oral administration of dried proanthocyanidin extract in an enteric coating for any purpose nor does Masquelier teach or even suggest that enteric protection is necessary or preferred for oral administration of the proanthocyanidin. Masquelier teaches administration of the proanthocyanidin extract in various vehicles for oral administration that do not protect against stomach acid (Masquelier at col. 6, lines 26-28). Thus, Masquelier does not suggest to the ordinarily skilled artisan that the proanthocyanidin extract should be formulated in an enteric coating, and, in fact, teaches away from the need for such a formulation.

Wursch relates to water insoluble tannins extracted from carob pods while the present invention is directed to water soluble proanthocyanidin polymers from *Croton* and *Calophyllum* species. Thus, the composition in Wursch is completely different and formulations of the Wursch composition have no bearing on the present formulations. In short, there is no combination to combine Wursch with Davenport because each teaches the use of very different compounds. Assuming, *arguendo*, that Wursch is even relevant, the formulations taught by Wursch are not aimed to protect the tannin composition but to sugar-

coat the composition so young children will ingest it. Unlike the teachings of the present specification, Wursch does not suggest the oral administration of any proanthocyanidin composition in an enteric coating, and does not teach the administration of tannins in any formulation in order to protect the tannins from the stomach environment.

Remington's is a compendium of pharmaceutical formulations and teaches a very large number of formulations, including enterically protected formulations as well as many, many more formulations that are not enterically protected. Without specific teachings or suggestion to pick that one formulation out of a substantial laundry list of formulations, there is no motivation to specifically choose any specific formulation for the composition, and therefore, Remington's in combination with any of the references does not render the claimed formulations obvious.

The Examiner also relies upon Applicants' statements that methods for making enteric formulations are well known in the art. However, these statements are merely cumulative to the disclosure of Remington's and do not in any way make up for the deficiencies in the cited references.

In sum, since Davenport is no longer available as prior art and the remained cited references, whether in combination with Davenport or not, do not teach or suggest the claimed formulations of the isolated proanthocyanidin polymer and actually either teach away from enteric protection of the polymer or are not relevant to formulations of the claimed proanthocyanidin polymer composition. Accordingly, the cited references, alone or in combination, do not render the pending claims obvious. Applicants respectfully request that the rejection be withdrawn.

CONCLUSION

Applicants believe that they have addressed all the issues outstanding in connection with the present application. Accordingly, reconsideration and an early allowance of the present application in view of the above remarks is respectfully requested.

Applicants respectfully request that the Examiner call the undersigned at 212-326-3939 if any questions or issues remain.

Respectfully submitted,

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